# The Impact of Obstructive Sleep Apnea on Aortic Disease in Marfan's Syndrome

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Abstract: Background: Aortic dissection is a life-threatening manifestation of Marfan's syndrome. Preliminary evidence suggests that obstructive sleep apnea (OSA) is associated with aortic disease in Marfan's syndrome. Objectives: To study the effect of OSA on aortic events in Marfan's syndrome. Methods: In patients with Marfan's syndrome, a sleep study was performed at baseline and OSA was defined as >5 events of apnea/hypopnea (A+H) per hour in bed. Operation because of progressive aortic dilatation and death because of aortic rupture were defined as 'aortic events'. Kaplan-Meier survival analyses were used to compare event-free survival in patients with and without OSA. Cox regression models were used to explore the effects of covariates on event-free survival. Results: Data from 44 patients (mean age 37.4 years, 30 females) were available for analysis; 15 patients (34.1%) had OSA. The median follow-up time was 29 (interquartile range 24-36) months. Five patients had an aortic event within the follow-up time. Median event-free survival was 51.6 months. Event-free survival was significantly shorter in patients with OSA compared to patients without OSA (p = 0.012). In univariate analysis, A+H was associated with aortic events [hazard ratio (HR) 1.09, 95% confidence interval (CI) 1.01-1.18, p = 0.023]. Taking the interaction between BMI and A+H into account increased the HR for A+H (HR 1.75, 95% CI 1.003-3.048, p = 0.049). This association was no longer significant when other covariates were forced into the multivariate analysis. Conclusions: These data suggest that aortic event-free survival may be shorter in patients with Marfan's syndrome and OSA compared to patients without OSA, but more data from well-designed studies are needed to prove this association.

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# The Impact of Obstructive Sleep Apnea on Aortic Disease in Marfan's Syndrome

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**Key Words**
Aorta · Marfan's syndrome · Obstructive sleep apnea · Survival

**Abstract**
***Background:*** Aortic dissection is a life-threatening manifestation of Marfan's syndrome. Preliminary evidence suggests that obstructive sleep apnea (OSA) is associated with aortic disease in Marfan's syndrome. ***Objectives:*** To study the effect of OSA on aortic events in Marfan's syndrome. ***Methods:*** In patients with Marfan's syndrome, a sleep study was performed at baseline and OSA was defined as >5 events of apnea/hypopnea (A+H) per hour in bed. Operation because of progressive aortic dilatation and death because of aortic rupture were defined as 'aortic events'. Kaplan-Meier survival analyses were used to compare event-free survival in patients with and without OSA. Cox regression models were used to explore the effects of covariates on event-free survival. ***Results:*** Data from 44 patients (mean age 37.4 years, 30 females) were available for analysis; 15 patients (34.1%) had OSA. The median follow-up time was 29 (interquartile range 24–36) months. Five patients had an aortic event within the follow-up time. Median event-free survival was 51.6 months. Event-free survival was significantly shorter in patients with OSA compared to patients without OSA ($p = 0.012$). In univariate analysis, A+H was associated with aortic events [hazard ratio (HR) 1.09, 95% confidence interval (CI) 1.01–1.18, $p = 0.023$]. Taking the interaction between BMI and A+H into account increased the HR for A+H (HR 1.75, 95% CI 1.003–3.048, $p = 0.049$). This association was no longer significant when other covariates were forced into the multivariate analysis. ***Conclusions:*** These data suggest that aortic event-free survival may be shorter in patients with Marfan's syndrome and OSA compared to patients without OSA, but more data from well-designed studies are needed to prove this association.



## Introduction

Marfan'syndrome is a connective tissue disease inherited in an autosomal dominant manner. It is caused by mutations in the FBN1 gene localized on chromosome 15q21, which encodes fibrillin-1, a glycoprotein that is the main component of microfibrils of the extracellular matrix. The prevalence of Marfan's syndrome is estimated to be between 1 and 3 per 10,000 individuals [1, 2]. The diagnosis primarily depends on a combination of major and minor clinical findings defined in the 'Ghent criteria'

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[3–5]. The hallmark clinical features are noted in the cardiovascular, ocular and skeletal systems.

Aortic root dilatation and subsequent dissection is the main cause of premature death in patients with Marfan's syndrome. Dilatation of the aortic root can begin in childhood or early adulthood and increases at an unpredictable rate [6, 7]. It is a matter of debate which factors contribute to a rapid progression of aortic root dilatation. Given its impact on survival, monitoring of patients with Marfan's syndrome is mainly directed toward the control of aortic disease.

There is a high prevalence of obstructive sleep apnea (OSA) in patients with Marfan's syndrome possibly due to craniofacial dysmorphism and an increased upper airway collapsibility [8–10]. There is also preliminary evidence for a causal link between OSA and aortic dilatation in patients with Marfan's syndrome [10–12]. Possible underlying pathophysiological mechanisms are post-apnea reflex sympathetic activation and consequent marked increases in blood pressure [13]. In addition, large negative intrathoracic pressure swings, which are produced during obstructive apneas, increase transaortic pressure and may therefore accelerate aortic dilatation [14, 15]. However, there are currently no data investigating the impact of OSA on the risk of needing aortic root replacement surgery or of death in Marfan's syndrome.

We have addressed this uncertainty by performing a prospective cohort study to evaluate if OSA contributes to the risk of future aortic root replacement or of dying from aortic root dissection in patients with Marfan's syndrome.

## Patients and Methods

*Patients and Controls*

Patients fulfilling the Ghent criteria [3–5] for Marfan's syndrome and attending their yearly clinical assessment at the Oxford Radcliffe Hospitals NHS Trust were asked to participate in the study. Subjects were eligible if they were between 18 and 75 years old, not pregnant, were not treated with continuous positive airway pressure (CPAP) and had not been operated on their aortic root previously. The study was approved by the Oxford Research Ethics Committee (REC No. 07/Q1607/6), and written informed consent was obtained from all participants.

*Measurements*

The following assessments were performed at baseline:

*Anthropometrics and Blood Pressure.* Height, weight and neck circumference were measured. Blood pressure and heart rate were measured in triplicate in the sitting position with a standard digital automatic monitor (Omron Healthcare, Kyoto, Japan). The mean value of three readings was used for analysis.

*Sleep Studies and Questionnaire.* Subjective sleepiness was assessed using the Epworth Sleepiness Scale questionnaire and home sleep studies were performed using the ApneaLink™ device (ResMed, MAP Medizin Technologie, Martinsried, Germany). The device records the patient's nasal respiratory pressure signal and finger oximetry during sleep; it has been validated as an accurate instrument to detect apnea, hypopnea and oxygen desaturation [16]. The recordings of the device were downloaded automatically with dedicated software (ResMed), followed by a manual scoring of apneas, hypopneas and oxygen desaturation. Apneas were defined as a cessation of airflow lasting >10 s and hypopneas as a reduction in airflow of at least 50% lasting >10 s, associated with a drop in oxygen saturation of >4%. OSA severity was quantified as the number events of apnea/hypopnea per hour of time in bed (A+H). The minimal criterion for an acceptable sleep study duration was 5 h (with nasal respiratory pressure and pulse-oximetry signal).

*Aortic Root Diameter Measurements.* In all patients with Marfan's syndrome, echocardiography was performed by the same cardiac ultrasound technician, who was not involved in the analysis of the data. Aortic root diameter was measured in parasternal long-axis view at end-diastole (peak of R wave on electrocardiogram) and at end-systole (T wave on electrocardiogram) by two-dimensional, M-mode echocardiography with a commercially available cardiac ultrasound system (Sonos 4500; Philips Healthcare, Guilford, UK), using a 3.5-MHz transducer. The diameter of the aorta was assessed at several levels: at the left-ventricular outflow tract, sinuses of Valsalva, supra-aortic ridge and at the proximal ascending aorta, 1–2 cm above the supra-aortic ridge, as described previously [17]. The maximal diameter of the aortic root from these four assessments and the maximal diameter corrected for body surface area were calculated [17].

*Follow-Up Assessments.* Follow-up assessments were scheduled according to routine clinical practice, usually at 1-year intervals, and included a medical history, measurement of anthropometrics as well as echocardiography.

*Outcome.* Operation because of progression of aortic root dilatation and death because of aortic root dissection/rupture were defined as an 'aortic event'. Survival time without an aortic event was defined as the primary outcome.

*Data Analysis*

Data are expressed as means (SD) unless otherwise stated. Statistical analyses were performed with STATA, College Station, Tex., USA (version 11.1 for Windows). In order to define OSA, a conventional threshold level of A+H >5/h was used. Differences in baseline characteristics between patients with and without OSA were assessed by independent t tests. Kaplan-Meier survival analyses were used to allow for variable follow-up times and to estimate the proportion of patients without an aortic event. The log-rank test was used to compare rates of aortic events between patients with and without OSA. Univariate Cox regression was applied to investigate the association between patient characteristics and survival without an aortic event. To further evaluate the independent association between aortic events and A+H, we used multivariable Cox regression modeling, including age, gender, baseline aortic diameter, body mass index (BMI), systolic blood pressure, antihypertensive medication and A+H as potential confounding covariates. A two-sided $p < 0.05$ was considered to be statistically significant.

**Table 1.** Patient characteristics at baseline

| | Patients with OSA (n = 15) | Patients without OSA (n = 29) | p value |
|---|---|---|---|
| Age, years | 44.0 (14.0) | 33.9 (13.4) | 0.025 |
| Males/females | 8/7 | 6/23 | 0.028 |
| BMI | 30.0 (7.0) | 22.6 (3.9) | <0.001 |
| Neck circumference, cm | 39.2 (2.7) | 34.7 (3.1) | <0.001 |
| Systolic blood pressure, mm Hg | 124.9 (13.7) | 121.4 (14.7) | 0.449 |
| Diastolic blood pressure, mm Hg | 78.6 (11.9) | 77.2 (12.0) | 0.723 |
| Heart rate, beats/min | 61.6 (8.5) | 64.1 (11.7) | 0.466 |
| Antihypertensive medication, % | 80.0 | 72.4 | 0.582 |
| Aortic diameter, cm | 4.3 (0.4) | 3.7 (0.6) | <0.001 |
| Aortic diameter/BSA | 2.0 (0.3) | 2.0 (0.3) | 0.747 |
| Aortic expansion rate, cm/year | 0.22 (0.68) | 0.07 (0.21) | 0.276 |
| A+H, events/h | 18.0 (11.3) | 2.4 (1.5) | <0.001 |
| ODI, n/h | 9.8 (7.9) | 2.1 (2.5) | <0.001 |
| Snoring, events/h | 88.6 (107.5) | 26.8 (33.8) | 0.008 |
| Time in bed, min | 408 (65) | 447 (81) | 0.101 |
| ESS | 7.6 (3.9) | 7.8 (5.2) | 0.899 |

Values are means (SD) were applicable. BSA = Body surface area; ODI = oxygen desaturation index; ESS = Epworth Sleepiness Score.

## Results

*Study Profile and Characteristics of the Participants*

Figure 1 shows the study profile. Patients with Marfan's syndrome were recruited from 41 unrelated families (no apparent relationships in their pedigree). Follow-up data from 44 patients with Ghent criteria-positive Marfan's syndrome and without previous operation on their aorta were available for analysis. Fifteen patients (34.1%) fulfilled the criteria of having OSA. Patients with OSA were older, had a higher BMI and a larger neck circumference than patients without OSA (table 1). The two groups were similar regarding their blood pressure, heart rate and baseline aortic diameter corrected for body surface area (table 1).

*Event-Free Survival*

The median (interquartile range) follow-up time after the baseline assessment was 29 (24–36) months. Within the follow-up period, 4 patients had aortic valve-sparing aortic root replacement and 1 patient died of aortic rupture. Median event-free survival was 51.6 months. As all patients with aortic events had OSA, event-free survival was significantly shorter in patients with OSA compared to patients without OSA (p = 0.012; fig. 2).

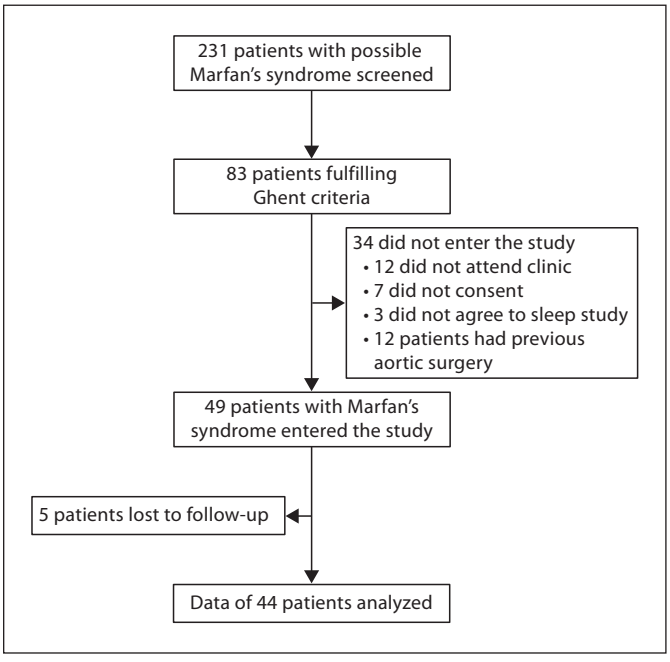


**Fig. 1.** Study profile.

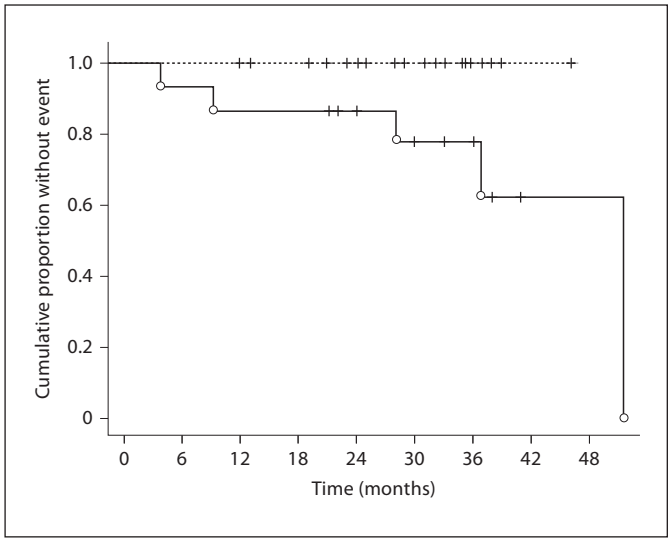


**Fig. 2.** Kaplan-Meier plot showing the proportion of patients without aortic events in subjects with OSA (——) and those without OSA (· · · · ·). Event-free survival was significantly shorter in patients with OSA compared to patients without OSA (p = 0.012).

**Table 2.** Univariate analysis

| | HR | SE | p value | 95% CI |
|---|---|---|---|---|
| Age | 1.05 | 0.04 | 0.192 | 0.98–1.13 |
| Gender (male = reference) | 5.53 | 6.41 | 0.140 | 0.57–53.64 |
| Baseline aortic diameter | 11.12 | 12.31 | 0.029 | 1.27–97.31 |
| BMI | 1.07 | 0.07 | 0.281 | 0.94–1.22 |
| Systolic blood pressure | 1.05 | 0.04 | 0.202 | 0.97–1.14 |
| A+H | 1.09 | 0.04 | 0.023 | 1.01–1.18 |
| Antihypertensive medication | 0.34 | 0.34 | 0.284 | 0.05–2.44 |

**Table 3.** Multivariate analysis

| A+H | HR | SE | p value | 95% CI |
|---|---|---|---|---|
| Model 1 | 1.12 | 0.06 | 0.028 | 1.01–1.24 |
| Model 2 | 1.75 | 0.50 | 0.049 | 1.00–3.05 |
| Model 3 | 2.04 | 1.25 | 0.246 | 0.61–6.80 |

Model 1 was controlled for BMI only, model 2 for BMI and an interaction term (BMI × A+H), and model 3 was controlled for BMI, BMI × A+H, age, gender, systolic blood pressure, antihypertensive medication and baseline aortic diameter.

In univariate analysis, higher A+H and higher aortic diameter at baseline were both associated with a significantly increased hazard ratio (HR) for aortic events (table 2).

Because being overweight is a major independent risk factor for OSA, we further investigated a potential modifying effect of BMI on the risk of aortic events due to an increased A+H by introducing an interaction term (i.e. BMI × A+H) in a bivariate Cox regression model (i.e. independent variables were A+H, BMI and its interaction term). Taking into account an interaction between BMI and A+H resulted in a considerable increase in HR for A+H (table 3). Further controlling for all potential confounders, regardless of whether significant in univariate analysis, revealed an unchanged HR for A+H; however, the association between aortic events and OSA did not remain statistically significant (table 3).

## Discussion

This is the first prospective cohort study providing data on the relationship between OSA and aortic events in patients with Marfan's syndrome. We found that patients with OSA had a significantly shorter event-free survival compared to patients without OSA, which suggests that OSA may be an important risk factor for aortic events. If this finding is confirmed in larger cohorts, then patients with Marfan's syndrome should be evaluated and possibly treated for OSA in order to reduce the risk of aortic complications.

Aortic dilatation and associated aortic dissection and rupture are still the main cause of morbidity and mortality in patients with Marfan's syndrome [18]. Thus, the prevention of aortic complications is of major concern for physicians caring for patients with Marfan's syndrome. As it is largely unknown which factors contribute to a rapid progression of aortic root dilatation in these patients, the prevention of aortic dissection and rupture currently rests on lifestyle advice, pharmacological treatments (e.g. β-blockers) and ultimately prophylactic aortic surgery [18–20]. Identification of any treatable risk factor for aortic complications in patients with Marfan's syndrome is thus of major scientific and clinical interest.

There is some preliminary evidence that OSA may be a risk factor for the development and progression of aortic aneurysms in patients with and without Marfan's syndrome [10–12, 21–23]. Kohler et al. [10] recently reported that the severity of OSA in patients with Marfan's syn-

drome is associated with an increased aortic root diameter and patients with OSA have a larger aortic root than patients without OSA. In the current study, we found that patients with Marfan's syndrome and OSA had a significantly shorter aortic event-free survival than patients without OSA. In univariate analysis, the only variables statistically significantly associated with a higher risk for aortic events were baseline aortic diameter and the severity of OSA (table 2). The HR of 1.09 for each additional A+H event per hour suggests that a patient with an A+H of 10 events/h has about a two times higher risk of needing aortic replacement surgery or of dying from aortic rupture for example.

Obesity is the most important factor in the pathogenesis of OSA, thus BMI and A+H are expected to be strongly interrelated. By adding an interaction term for BMI and A+H to the multivariate analysis, the HR for A+H increased considerably to 1.75, suggesting that particularly Marfan patients who are overweight and have OSA may be at high risk of having aortic complications. This is supported by the fact that all 5 patients with aortic events had OSA, and 4 of the 5 patients also had BMI above the median BMI of the cohort (data not shown). Although HR (1.76) was unaffected by additional correction for age, gender, baseline aortic diameter and blood pressure in multivariate analysis, the association between A+H and aortic events did not remain statistically significant. This is most likely due to the relatively small number of patients studied given the limited number of aortic events observed. Thus, further studies investigating the effect of OSA on aortic events in larger cohorts of Marfan patients are needed.

The findings of the current study suggest that obese patients with Marfan's syndrome should perhaps be evaluated for OSA and may benefit from weight reduction or CPAP. This is corroborated by the findings of two case reports in which treatment of OSA with CPAP was associated with attenuation of aortic root dilatation in 3 patients with Marfan's syndrome [11, 12]. However, more data from interventional studies investigating the effect of CPAP on aortic dilatation and aortic events are needed before CPAP therapy can be recommended as a therapy to improve outcome in patients with Marfan's syndrome and OSA.

To date, the underlying mechanisms through which OSA may promote aortic dilatation are not clear. OSA has been shown to be associated with increased diurnal blood pressure as well as with recurrent pronounced surges in blood pressure during apneic events [24], which is the proposed main risk factor for aortic dilatation and dissection [25]. In addition, obstructive apneas are associated with repeated inspiratory effort against the collapsed pharynx causing recurrent large negative intrathoracic pressures (sometimes as low as –80 mm Hg) and thereby producing radial forces on intrathoracic structures including the ascending aorta [26]. This hypothesis is supported by the findings of Peters et al. [27, 28] who reported increased aortic diameters during obstructive apnea in an animal model. In healthy humans, experimentally simulated obstructive A+H has also been shown to lead to an acute increase in proximal aortic diameter [15]. Furthermore, Sampol et al. [21] found that non-Marfan patients with dissection of the thoracic aorta had a higher index of A+H than well-matched hypertensive control subjects without dissection, suggesting that OSA may be a risk factor for aortic dissection. Thus, the current body of evidence suggests that intrathoracic pressure swings and acute blood pressure rises, rather than intermittent hypoxia, may be the most important mechanisms underpinning the association between OSA and thoracic aortic disease. This is also supported by our previous work on OSA and aortic dilatation in patients with Marfan's syndrome where we found a much stronger correlation between apneas and aortic root diameter than between oxygen indices and aortic root diameter [10].

The current study has some limitations which need to be mentioned. We did not use full polysomnography, which would have been the gold standard for quantification of sleep-disordered breathing; however, this is very unlikely to have biased outcome in any way. The number of patients with Marfan's syndrome in this study without previous aortic root replacement is relatively small, given the number of aortic events observed during the follow-up period. Thus, further prospective cohort studies including a larger number of patients with Marfan's syndrome will be needed to corroborate our findings. However, as Marfan's syndrome is a rare disorder and the existing cohorts of these patients tend to be small, such a prospective study would possibly need a multicenter design. Finally, data from interventional studies looking at the effect of CPAP on aortic dilatation and aortic events are required before a causal relationship between OSA and aortic disease can be established.

In conclusion, we have shown that in a cohort of patients with Marfan's syndrome having OSA may be associated with a shorter aortic event-free survival compared to patients without OSA. The risk for aortic events seems to be primarily elevated in patients with Marfan's syndrome who are overweight and have OSA. These findings

suggest that overweight patients with Marfan's syndrome should be evaluated and possibly treated for OSA in order to reduce the risk of aortic complications. However, data from randomized interventional trials are needed to definitely prove this relationship.


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## Financial Disclosure and Conflicts of Interest

None of the authors has a competing interest regarding this work.

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